Breast Cancer Research and Treatment **83:** 77–86, 2004.

Report

Is male breast cancer similar or different than female breast cancer?

William F. Anderson[1], Michelle D. Althuis[2], Louise A. Brinton[2], and Susan S. Devesa[2]
[1]*NCI/Division of Cancer Prevention;* [2]*NCI/Division of Cancer Epidemiology and Genetics, Bethesda, MD, USA*

Key words: age-frequency distribution, estrogen receptor expression, incidence rates, male breast cancer

Summary

Objective. To determine if male breast carcinogenesis was similar to its more common female counterpart, we compared incidence patterns among men and women with breast cancer.

Methods. Breast cancer records were obtained from the SEER database. Women were stratified by age <50 and ≥ 50 years to simulate premenopausal and postmenopausal breast cancer.

Results. Age-adjusted incidence trends were stable among men but increased among women. Male to female breast cancer ratio was higher for blacks than for whites. Favorable prognostic factors reflective of tumor biology (*nuclear grade and hormone receptor expression*) were more common for men and postmenopausal women than for premenopausal women. For example, low nuclear grade, estrogen and progesterone receptor-positive expression were more common among men and postmenopausal women than among premenopausal women. The age-specific incidence rate curve for men increased steadily for all ages with a constant slope. On the other hand, age-specific rates for women increased rapidly until age 50 years then rose at a slower rate for postmenopausal women. Age-frequency distribution for male breast cancer was unimodal, with peak incidence at age 71 years. Age-frequency distribution for women was bimodal with early-onset and late-onset incidence at 52 and 71 years, respectively.

Conclusions. Gender-specific incidence trends differed, most likely reflective of female-related changes in surveillance and/or reproductive risk factors. On the other hand, similar prognostic factor profiles reflective of tumor biology, age-specific incidence rate patterns, and age-frequency distributions suggested that male breast cancer was more like postmenopausal than premenopausal female breast cancer.

Introduction

Cancer of the vestigial male breast is a rare disease in all parts of the world, accounting in the United States for $<0.1\%$ of male cancers and $<1\%$ of all breast cancers [1]. With fewer than 1500 new cases diagnosed annually in this country, our understanding and treatment strategies for male breast cancer are generally extrapolated from our knowledge of female breast cancer. However, if male and female breast carcinogenesis were the same disease processes, we might expect similar incidence patterns [2]. Some well-established facts suggest otherwise.

For example, incidence rate temporal trends for male breast cancer have remained stable for decades while rates for female breast cancer have increased worldwide [3, 4]. Age-specific incidence rate curves for men increase steadily at all ages [5, 6]; whereas rates for women increase rapidly until age 50 years then rise more slowly for older women [7]. Age-specific incidence rates for breast cancers defined by ER expression differ for women [8–10], but have not been established for men.

In a previous study, we compared female breast cancer defined by ER expression [10]. In this analysis, we have expanded our original observations: (1) to compare breast cancer incidence patterns for men and women, (2) to compare breast cancer incidence patterns defined by ER expression for men and women, (3) to compare male breast cancer to

premenopausal and postmenopausal female breast cancers, and (4) to assess whether these patterns provided new etiologic clues.

Material and methods

We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Incidence Public-Use database (November 2002 submission) to obtain male and female breast cancer records diagnosed during the years 1973–2000, recently covering approximately 14% of the US population [11]. The SEER program provided overlapping 9 and 12 Registry Databases. The 9 Registry Database collected incidence data for the years 1973–2000 from SEER's original catchment regions, including registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. The 12 Registry Database collected information for the years 1992–2000 from SEER's original 9 registries plus Los Angeles, San Jose-Monterey, and the Alaskan Native Tumor registries. Although operative for fewer years than the 9 Registry Database, the 12 Registry Database provided more detailed information for tumor characteristics and hormone receptor expression. For example, SEER did not collect information concerning certain tumor features such as tumor size, axillary lymph nodal status, and nuclear grade until 1988, and did not collect data regarding hormone receptor expression until 1990.

Incidence rates with standard errors (SE) for males and females with breast cancer were calculated using SEER stat 5.0.20 [11]. Female cases were divided into early-onset (<50 years) and late-onset (≥50 years) breast cancers to simulate premenopausal and postmenopausal disease. All rates were age-adjusted to the 2000 US standard population and expressed per 100,000 man-years or woman-years.

Long-term age-adjusted incidence trends were derived from the SEER 9 Registry Database, and then plotted on a log-linear graph to show temporal changes from 1973 to 2000. From the 12 Registry Database, we obtained rates for certain patient demographics and tumor characteristics, including age-at-diagnosis, race, tumor size, axillary lymph nodal status, nuclear grade, estrogen receptor (ER) expression, progesterone receptor (PR) expression, and joint ERPR expression.

SEER's tumor grading conformed to the International Classification of Diseases for Oncology – 2nd edition (ICDO-2) [12]. We combined grades I (well differentiated) with II (moderately differentiated) and grades III (poorly differentiated) with IV (undifferentiated) into low and high tumor grades, respectively. Because no centralized laboratory was used to determine hormone receptor expression, each SEER registry coded estrogen receptor (ER) and progesterone receptor (PR) expression as positive, negative, missing, or unknown. We combined missing and unknown data into one group, designated as unknown.

Age-specific incidence rate curves were charted on a log–log scale as originally described by Armitage and Doll [13]. We fitted these log–log age-specific rate curves with Poisson regression analyses to quantify slope changes and to assess random variation at the midpoint of 5-year-age groups, with the focus of our inference on change-points [8, 9]. Age-frequency distribution curves were plotted as age-frequency

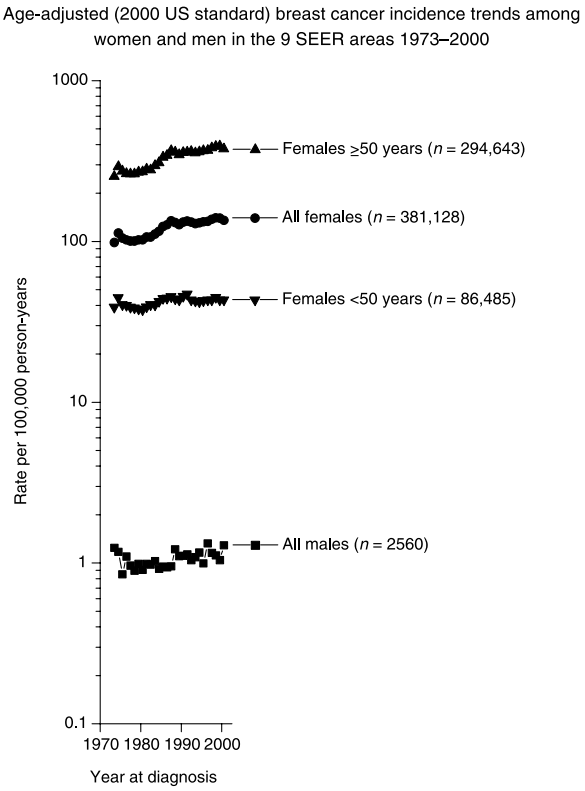

Figure 1. Age-adjusted (2000 US standard) breast cancer incidence temporal trends in SEER's nine registries, collected during the years 1973–2000.

Table 1. Male and female breast cancer cases from SEER's 12 Registry Database, diagnosed during the years 1992–2000[a]

Variable	Males (n = 1,456, rate = 1.15 (SE = 0.03))				Females <50 years (n = 50,730, rate = 42.6 (SE = 0.19))				Females ≥50 years (n = 165,334, rate = 367.9 (SE = 0.91))			
	n	Rate	SE	RR	n	Rate	SE	RR	n	Rate	SE	RR
Demographics												
Age												
<50	163	0.1	0.01	1.0	50,730	42.6	0.19	1.0	50,730	42.6	0.19	1.0
50–59	263	1.7	0.11	12.2					45,517	280.5	1.32	6.6
60–69	384	3.7	0.19	26.3					46,467	386.7	1.80	9.1
70–79	408	5.6	0.28	40.3					46,692	472.1	2.19	11.1
80+	238	7.8	0.51	55.5					26,658	434.3	2.66	10.2
Race												
White	1,189	1.1	0.03	1.0	39,202	43.0	0.22	1.0	141,578	386.5	1.03	1.0
Black	171	1.8	0.15	1.6	5,914	44.4	0.58	1.0	12,250	321.9	2.92	0.8
Other	77				5,228				10,638			
Unknown	19				386				868			
Tumor features												
Tumor size												
>2.0 cm	558	0.5	0.02	1.0	19,587	16.3	0.12	1.0	48,467	107.8	0.49	1.0
≤2.0 cm	745	0.6	0.02	1.3	26,030	22.0	0.14	1.3	100,067	223.2	0.71	2.1
Unknown	153				5,113				16,800	36.9		
Lymph nodes												
LN-positive	501	0.4	0.02	1.0	19,087	15.9	0.12	1.0	41,656	94.1	0.46	1.0
LN-negative	778	0.6	0.02	1.6	27,419	23.1	0.14	1.4	102,365	228.1	0.72	2.4
Unknown	177				4,224				21,313			
Tumor grade												
High	463	0.4	0.02	1.0	22,414	18.6	0.13	1.0	47,656	107.2	0.49	1.0
Low	717	0.6	0.02	1.5	20,139	17.1	0.12	0.9	83,288	185.2	0.64	1.7
Unknown	276				8,177				34,390			
Hormone receptors												
ER												
ER-negative	97	0.1	0.01	1.0	13,649	11.3	0.10	1.0	25,334	57.5	0.36	1.0
ER-positive	932	0.7	0.03	10.1	26,152	22.1	0.14	1.9	101,990	226.7	0.71	3.9
Unknown	427				10,929				38,010			
PR												
PR-negative	194	0.1	0.01	1.0	14,553	12.1	0.10	1.0	39,386	88.4	0.45	1.0
PR-positive	792	0.6	0.02	4.2	24,136	20.4	0.13	1.7	83,392	185.7	0.65	2.1
Unknown	470				12,041				42,556			
Joint ERPR												
ER−PR−	69	0.05	0.006	1.0	11,241	9.3	0.09	1.0	21,536	48.9	0.33	1.0
ER−PR+	22	0.02	0.004	0.3	2,014	1.7	0.04	0.2	3,084	7.0	0.13	0.1
ER+PR−	122	0.09	0.009	1.8	3,191	2.7	0.05	0.3	17,546	38.9	0.29	0.8
ER+PR+	768	0.61	0.022	11.7	21,909	18.5	0.13	2.0	79,995	118.0	0.63	2.4
Unknown	475				12,375				43,173			

[a]Key: SE, standard error; Rate, age-adjusted (2000 US standard) incidence rate expressed per 100,000 man- or woman-years; RR, rate ratio where a given characteristic is compared to a reference value with an assigned RR of 1.0; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Black and white male breast cancer cases from SEER's 12 Registry Database, diagnosed during the years 1992–2000[a]

Variable	Black males ($n = 171$, median age = 64 years, rate = 1.8 (SE = 0.15))				White males ($n = 1{,}189$, median age = 68 years, rate = 1.1 (SE = 0.03))			
	n	Rate	SE	RR	n	Rate	SE	RR
Age								
Age								
<50	21	0.2	0.04	1.0	122	0.1	0.01	1.0
50–59	45	3.4	0.50	18.0	200	1.6	0.11	12.1
60–69	39	4.6	0.73	24.3	320	3.8	0.21	28.4
70–79	39	8.0	1.28	42.6	350	5.8	0.31	43.6
80+	27	15.5	3.01	82.8	197	7.5	0.54	56.7
Tumor features								
Tumor size								
>2.0 cm	84	0.9	0.10	1.0	444	0.4	0.02	1.0
≤2.0 cm	70	0.7	0.09	0.8	624	0.6	0.02	1.3
Unknown	17				121			
Lymph nodes								
LN-positive	65	0.6	0.08	1.0	408	0.4	0.02	1.0
LN-negative	75	0.8	0.10	1.2	658	0.6	0.03	1.6
Unknown	31				123			
Tumor grade								
High	62	0.7	0.09	1.0	378	0.4	0.02	1.0
Low	75	0.8	0.09	1.1	596	0.6	0.02	1.6
Unknown	34				215			
Hormone receptors								
ER								
ER-negative	18	0.2	0.04	1.0	72	0.1	0.01	1.0
ER-positive	92	1.0	0.11	5.6	788	0.8	0.03	11.3
Unknown	61				329			
PR								
PR-negative	34	0.3	0.05	1.0	147	0.1	0.01	1.0
PR-positive	72	0.8	0.10	2.6	674	0.6	0.03	4.7
Unknown	65				368			
Joint ERPR								
ER−PR−	13	0.12	0.036	1.0	51	0.05	0.007	1.0
ER−PR+	5	0.05	0.024	0.4	15	0.01	0.004	0.3
ER+PR−	21	0.18	0.041	1.5	93	0.09	0.009	1.9
ER+PR+	66	0.73	0.096	6.1	658	0.63	0.019	13.5
Unknown	66				372			

[a]Key: Median age-at-diagnosis, SE, standard error; Rate, age-adjusted (2000 US standard) incidence rate expressed per 100,000 man- or woman-years; RR, rate ratio where a given characteristic is compared to a reference value with an assigned RR of 1.0; ER, estrogen receptor; PR, progesterone receptor.

density functions as previously described [10, 14]. Briefly, the age-frequency density function represented 'smoothed' estimates of the age-at-diagnosis frequency histogram where the area under the plot included 100% of breast cancer cases, that is, density function × 100 = percent.

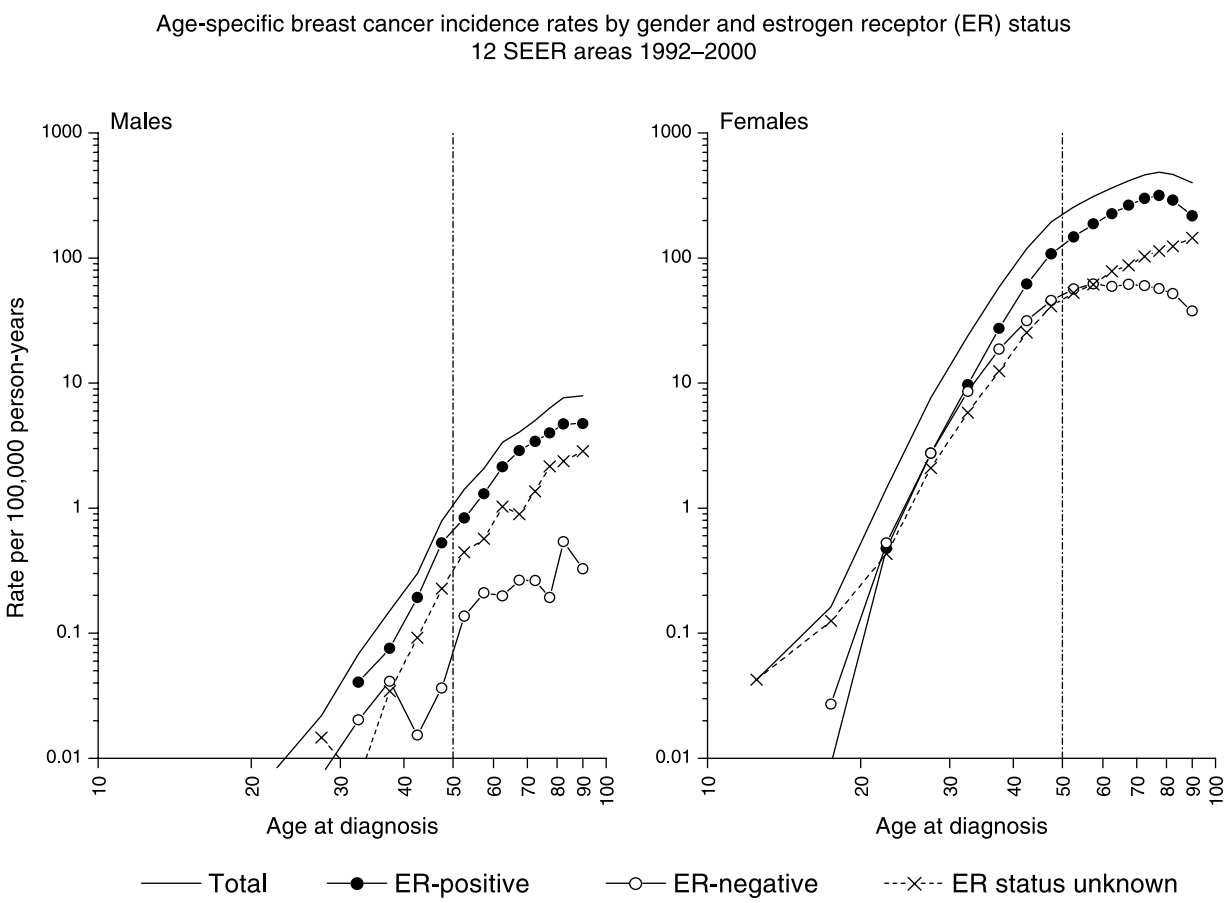

Figure 2. Age-specific breast cancer incidence rates in SEER 12 registries stratified by gender and estrogen receptor status among male and female breast cancer cases, collected during the years 1992–2000.

Results

SEER's 9 and 12 Registry Databases included 383,688 and 217,520 invasive breast cancer cases, respectively. Median ages-at-diagnosis were 67 years for men and 62 years for women in both databases. The frequency of male to female breast cancer cases in SEER was 1% for blacks and 0.7% for whites in both databases.

SEER 9 Registry Database (1973–2000)

Breast cancer incidence rates were stable among men over the last three decades, ranging from 0.85 to 1.3 per 100,000 man-years (Figure 1). On the other hand, rates rose nearly 38% among women overall, ranging from 98 to 135 per 100,000 woman-years during the same time period, with the majority of the increase occurring during the 1980s. Most of the temporal increase for women occurred in females ≥50 years, increasing 48% from 254 to 376 per 100,000 woman-years. On the other hand, rates for <50 years were fairly constant, ranging from 39 to 43 per 100,000 woman-years.

SEER 12 Registry Database (1992–2000)

Breast cancer incidence rates for certain patient demographics, tumor features, and hormone receptor expression among men, females <50 years, and females ≥50 years were derived from SEER's 12 Registry Database (Table 1). Approximately three-quarters of all women with breast cancer were ≥50 years of age-at-diagnosis. Rates for males with breast cancer increased steadily for each decade of life, with the highest rate of 7.8 per 100,000 man-years occurring at 80+ years (RR = 55.5, relative to men age <50 years). Incidence rates were greatest among women during age 70–79 years (RR = 11.1). Rate ratios for blacks compared to whites were higher for men (RR = 1.6)

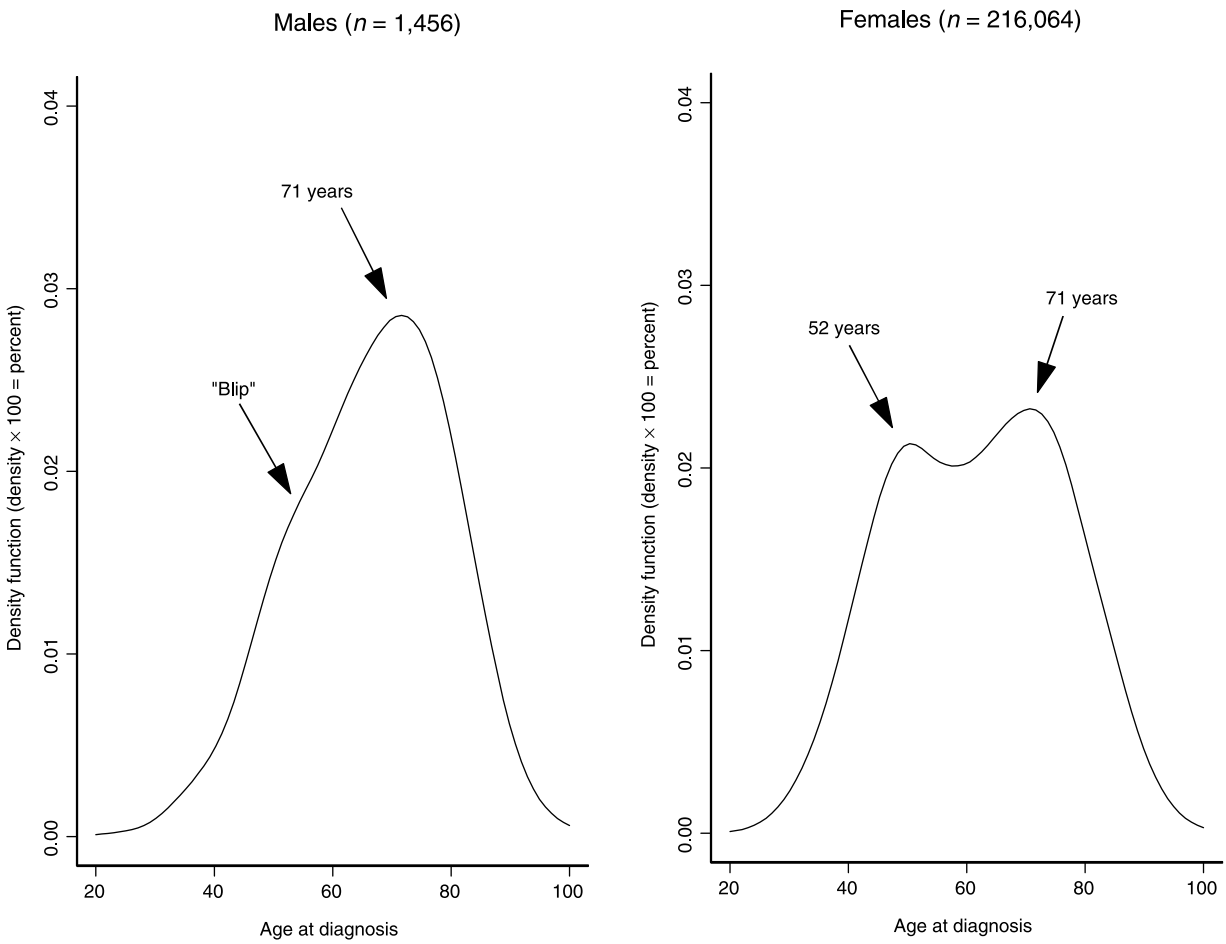

Figure 3. Age-frequency distribution function derived from SEER's 12 registries for male and female breast cancers, collected during the years 1992–2000.

and younger women (RR = 1.0) than for older women (RR = 0.8).

Tumor size and lymph nodal status (*prognostic factors reflective of staging*) were more favorable for older women (≥50 years) than for either men or younger women (<50 years). For example, RR for small to large tumors (≤2.0 cm to >2.0 cm) was greater for older women (RR = 2.1) than for men or for younger women (RR = 1.3). We observed a similar pattern for LN-negative to LN-positive tumors. On the other hand, RR for tumor grade and hormone receptor expression (*prognostic factors reflective of tumor biology*) was more favorable for men and older women than for younger women. That is, RR for low to high nuclear grade was 1.5 and 1.7 for men overall and older women compared to 0.9 for younger women. RR for ER-positive to ER-negative expression was 10.1 for men and 3.9 for older women compared to 1.9 for younger women. We observed similar patterns for PR and joint ERPR expression.

Breast cancer incidence rates for certain patient demographics, tumor features, and hormone receptor expression among black and white men with breast cancer are shown in Table 2. RR for black to white male breast cancer was 1.6 that is, 1.8 to 1.1 per 100,000 man-years. Male breast cancer incidence rates were higher among blacks than whites for all ages. Black compared to white male cancer was characterized by worse prognostic factor profiles with large tumor sizes, positive LN status, high nuclear grade, and negative hormone receptor expression. For example, RR for ER-positive to ER-negative expression was 5.6 for blacks and 11.3 for whites.

Male and female age-specific incidence rate curves were presented in Figure 2 for breast cancers overall as well as for breast cancers defined by ER expres-

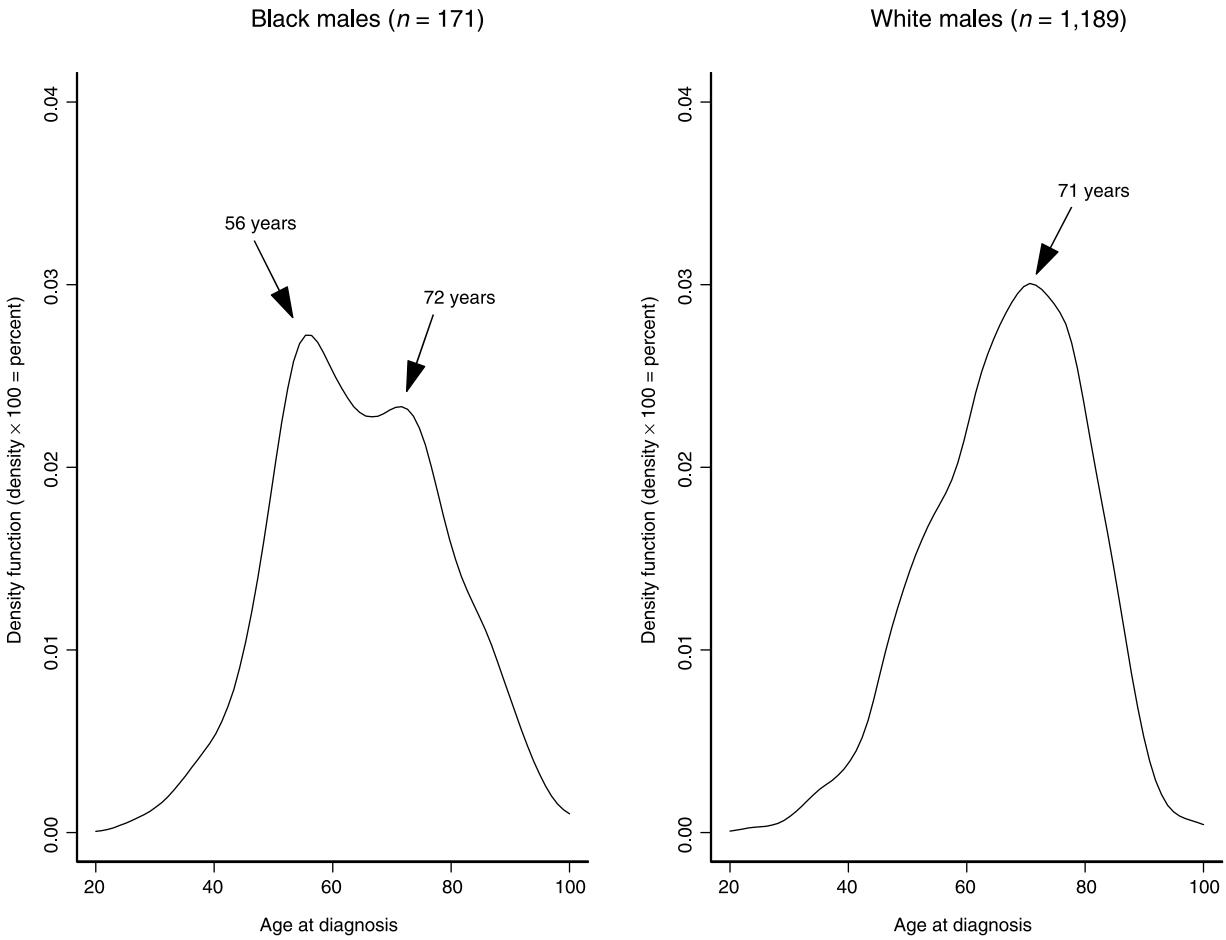

Figure 4. Age-frequency distribution function derived from SEER's 12 registries for black and white male breast cancers, collected during the years 1992–2000.

sion. Total (or overall) age-specific rates for males with breast cancer increased steadily at all ages with a constant slope between 4 and 5. On the other hand, total age-specific rates for females increased rapidly until age 50 years with an initial slope of 5–6, and then continued to rise more slowly with a final slope of approximately 2. Rates for ER-negative tumors among women increased rapidly until age 50 years, then flattened and possibly declined after age 70–75 years. On the other hand, ER-positive tumors for women increased rapidly until age 50 years, and then rose more slowly for older women, as did total rates for females. ER-positive age–rate curves among males increased steadily at all ages. The pattern for ER-negative tumors among males was less clear due to small sample size; but these rates also appeared to increase, albeit at a slower rate than ER-positive tumors.

PR expression did not alter the basic shape of the age–rate curve as defined by ER expression. For example, joint ER-positive tumors in women (ER + PR + or ER + PR −) continued to rise after 50 years, whereas joint ER-negative tumors in women (ER − PR − or ER − PR +) failed to rise after 50 years (graph not shown). Joint ERPR patterns for males could not be determined due to small sizes for some joint receptors.

Gender-specific age-frequency density plots were displayed in Figure 3. Notwithstanding a very small blip at approximately age 50 years, male breast cancer demonstrated unimodal age-frequency distribution with a peak incidence at age 71 years. On the other hand, female breast cancer demonstrated bimodal age-frequency distribution, with early-onset and late-onset peak incidence at 52 and 71 years,

respectively. Age-frequency distributions for black and white male breast cancers were shown in Figure 4. In contrast to unimodal age-frequency distribution among white men, black men with breast cancer had bimodal age-frequency distribution with early-onset and late-onset peak frequencies of 56 and 71 years, respectively.

Discussion

Gender-specific temporal differences in age-adjusted incidence trends (Figure 1) most likely resulted from female-related changes in surveillance, reproductive risk factors and/or exposures. On the other hand, similar (1) age-frequency distribution, (2) prognostic factor profiles reflective of tumor biology (*nuclear grade and hormone receptor expression*), and (3) age-specific incidence rate patterns suggested that male breast cancer was more like postmenopausal than premenopausal female breast cancer.

First, unimodal age-frequency distribution for male breast cancer was more like late-onset (postmenopausal) than early-onset (premenopausal) female breast cancer (Figure 3). In contrast to unimodal male breast cancer, bimodal or two female breast cancer types have long-been suspected [2, 15]. The first was early-onset and dependent upon hormonal exposures operating early in reproductive life, with a peak incidence of approximately age 50 years. The second was late-onset and dependent upon accumulated lifetime hormonal and/or environmental exposures, with a peak incidence of approximately age 70 years. In our previous analysis among female breast cancer cases [10], we conceptualized these two breast cancer types as juxtaposed early-onset and late-onset breast cancer populations. Notably, unimodal male breast cancer appeared virtually super imposable with late-onset female breast cancer.

Notwithstanding a nearly imperceptible blip at approximately age 50 years (Figure 3); there was no male counterpart to early-onset female breast cancer, until we stratified by black–white race (Figure 4). In contrast to white men, black men with breast cancer had a predominant early-onset peak incidence at age 56 years. Brunet et al. identified bimodal male breast cancer in a French cohort [16]; but to our knowledge, this phenomenon has not been described in any other male population.

Second, favorable prognostic factor profiles were more common for male breast cancer and postmenopausal than for premenopausal female breast cancer (Table 1). That is, breast cancers in men and postmenopausal women were comparatively indolent with low grade and hormone receptor-positive expression. On the other hand, breast cancers among premenopausal women tended to be biologically aggressive, with high nuclear grade and hormone receptor-negative expression.

Similar to premenopausal women, black men developed early-onset aggressive breast cancer phenotypes (Table 2). Male breast cancer overall was 60% (RR = 1.6) more common among blacks than whites. Worldwide, the frequency of male to female breast cancer cases varies from 7 to 14% in sub-Saharan Africa to <1% in white Western populations [17, 18]. Increased breast cancer incidence among black men is especially intriguing given decreased overall breast cancer incidence among black women. For example, overall breast cancer incidence is 15% lower in SEER for black compared to white women. However, the black to white incidence rate ratio is reversed for women younger than age 40 years, where breast cancer rates are 10–40% higher for blacks than whites [19, 20]. In addition to developing more early-onset disease than do white women, black women more commonly develop aggressive breast cancer phenotypes, as do black men. Ethnic-related breast cancer variation among black women has been attributed to higher tumor grade, negative hormone receptor expression, advanced stage-at-diagnosis, reduced access to health care, socio-cultural factors, etc. [21–23]. These same biologic and non-biologic factors may be operative for black men. Further analytic studies are clearly needed to better understand black–white ethnic disparity for both male and female breast cancers.

Third, the age-specific incidence rate curve for male breast cancer increased continuously with aging as did the rate curve for postmenopausal female breast cancer. Indeed, age-specific breast cancer rates among men increased in step with calendar time yielding a linear log–log rate curve with a slope between 4 and 5 (Figure 2), a pattern consistent with hormone independent epithelial carcinogenesis [24]. Admittedly, excessive hormonal exposures have been implicated for some male breast cancers resulting from Klinefelter's syndrome, gynecomastia, obesity, testicular and/or liver dysfunction [17, 25–27], but these high-risk conditions might only account for a small portion of male breast cancer cases. In this regard, it may be relevant that mean ages-at-diagnosis

are younger for Klinefelter's syndrome (58 years) and gynecomastia (55.4 years) [17, 27] than were mean and/or median (67 years) ages-at-diagnosis for male breast cancer in the SEER program. Possibly, the small blip at approximately age 50 years in the age-frequency distribution function for male breast cancer overall (Figure 3) might reflect a minor component of early-onset hormone-dependent breast cancer among men with strong genetic risk [28]. Notably, male breast cancer has been associated with hereditary mutations in the *BRCA2* but less frequently with the *BRCA1* gene [29–31]. The association of male breast cancer with *BRCA* mutations may partly explain the relationship of male breast cancer with Jewish ancestry [17, 32].

Notably, age-specific rates for women defined by ER expression diverged, suggesting different etiologies for ER-positive and ER-negative breast cancers (Figure 2). Paradoxically, incidence rates that stabilized after age 50 years suggested that endogenous hormonal exposures had greater impact upon early-onset ER-negative than upon late-onset ER-positive tumors [8–10]. Rates for males were largely unaffected by ER expression; but caution is required in interpreting these rates given that there were only 97 males with ER-negative breast cancers.

In conclusion, male and female breast carcinogenesis may reflect the consequence of two risk factor profiles, which are relatively dependent or independent upon endogenous hormonal exposures operating early in reproductive life [10, 33, 34]. Population-based incidence patterns implied an important etiologic link for early-onset hormonal events for ER-negative tumors and premenopausal female breast cancer. On the other hand, accumulated lifetime exposures appeared more important for ER-positive tumors, postmenopausal female breast cancer, and male breast cancer overall.

Limitations of our study included incomplete and non-standardized data for estrogen receptor expression as well as the lack of data on individual menopausal status and other well-established risk factors, which could impact results. However, the findings in this large-scale dataset that were broadly representative of the US population suggested that male breast cancer was similar to postmenopausal female breast cancer. Although it may seem counterintuitive, late-onset ER-positive tumors in both men and women appeared less dependent upon endogenous hormonal factors than did early-onset ER-negative breast cancers. Notably, black–white ethnic disparity appears to exist for both male as well as female breast cancers. A better understanding of these complicated age-related incidence patterns may further elucidate fundamental etiologic mechanisms for all breast cancers.

References

1. Jemal A, Murray T, Samuels A et al.: Cancer statistics, 2003. CA Cancer J Clin 53: 5–26, 2003
2. Moolgavkar SH, Lee JA, Hade RD: Comparison of age-specific mortality from breast cancer in males in the United States and Japan. J Natl Cancer Inst 60: 1223–1225, 1978
3. Parkin DM, Bray FI, Devesa SS: Cancer burden in the year 2000. The global picture. Eur J Cancer 37(Suppl 8): S4–S66, 2001
4. Levi F, Lucchini F, La Vecchia C: Epidemiology of male breast cancer. Eur J Cancer Prev 11: 315–318, 2002
5. Ewertz M, Holmberg L, Karjalainen S et al.: Incidence of male breast cancer in Scandinavia, 1943–1982. Int J Cancer 43: 27–31, 1989
6. Thomas DB: Breast cancer in men. Epidemiol Rev 15: 220–231, 1993
7. Clemmesen J: Carcinoma of the breast. Br J Radiol 21: 583–590, 1948
8. Yasui Y, Potter JD: The shape of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Contr 10: 431–437, 1999
9. Tarone RE, Chu KC: The greater impact of menopause on ER− than ER+ breast cancer incidence: a possible explanation (United States). Cancer Causes Contr 13: 7–14, 2002
10. Anderson WF, Chatterjee N, Ershler WB et al.: Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. Breast Cancer Res Treat 76: 27–36, 2002
11. SEER, 2003
12. Percy C, Holten VV, Muir C: International Classification of Diseases for Oncology. World Health Organization, Geneva, 1990
13. Armitage P, Doll R: The age distribution of cancer and a multistage theory of carcinogenesis. Br J Cancer 8: 1–12, 1954
14. Anderson WF, Chu KC, Chatterjee N et al.: Tumor variants by hormone receptor expression in white patients with node-negative breast cancer from the Surveillance, Epidemiology, and End Results database. J Clin Oncol 19: 18–27, 2001
15. von Pirquet C: Allergie des Lebensalters, die bosartigen Geschwulste ('Allergy of age, the Malignant Tumors'). Thieme Verlag, Leipzig, Germany, 1930
16. Brunet M, Hucher M, Boutros F et al.: [Is there any bimodality of the age distribution of male mammary cancer (author's transl)?]. Rev Epidemiol Sante Publique 24: 405–413, 1976
17. Sasco AJ, Lowenfels AB, Pasker-de Jong P: Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. Int J Cancer 53: 538–549, 1993
18. Amir H, Makwaya CK, Moshiro C et al.: Carcinoma of the male breast: a sexually transmitted disease? East Afr Med J 73: 187–190, 1996
19. Brinton LA, Benichou J, Gammon MD et al.: Ethnicity and variation in breast cancer incidence. Int J Cancer 73: 349–355, 1997

20. Hankey BF, Miller B, Curtis R et al.: Trends in breast cancer in younger women in contrast to older women. J Nat Cancer Inst Monogr 16: 7–14, 1994
21. Chen VW, Correa P, Kurman RJ et al.: Histological characteristics of breast carcinoma in blacks and whites. Cancer Epidemiol Biomarkers Prev 3: 127–135, 1994
22. Eley JW, Hill HA, Chen VW et al.: Racial differences in survival from breast cancer. Results of the national cancer institute black/white cancer survival study. JAMA 272: 947–954, 1994
23. Henson DE, Chu KC, Levine PH: Histologic grade, stage, and survival in breast carcinoma: comparison of African American and Caucasian women. Cancer 98: 908–917, 2003
24. Pike MC, Krailo MD, Henderson BE et al.: 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature 303: 767–770, 1983
25. Keller AZ: Demographic, clinical and survivorship characteristics of males with primary cancer of the breast. Am J Epidemiol 85: 183–199, 1967
26. Hsing AW, McLaughlin JK, Cocco P et al.: Risk factors for male breast cancer (United States). Cancer Causes Contr 9: 269–275, 1998
27. Rose DP: Endocrine epidemiology of male breast cancer (review). Anticancer Res 8: 845–850, 1988
28. Everson RB, Li FP, Fraumeni Jr JF et al.: Familial male breast cancer. Lancet 1: 9–12, 1976
29. Wooster R, Neuhausen SL, Mangion J et al.: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12–13. Science 265: 2088–2090, 1994
30. Stratton MR, Ford D, Neuhasen S et al.: Familial male breast cancer is not linked to the BRCA1 locus on chromosome 17q. Nat Genet 7: 103–107, 1994
31. Thorlacius S, Tryggvadottir L, Olafsdottir GH et al.: Linkage to BRCA2 region in hereditary male breast cancer. Lancet 346: 544–545, 1995
32. Mabuchi K, Bross DS, Kessler II: Risk factors for male breast cancer. J Natl Cancer Inst 74: 371–375, 1985
33. Narod SA: Modifiers of risk of hereditary breast and ovarian cancer. Nature Rev Cancer 2: 113–123, 2002
34. Hamilton AS, Mack TM: Puberty and genetic susceptibility to breast cancer in a case-control study in twins. N Engl J Med 348: 2313–2322, 2003

Address for offprints and correspondence: William F. Anderson, MD MPH, NCI/Division of Cancer Prevention, EPN, Room 2144, 6130 Executive Blvd, Bethesda, MD 20892-7317, USA; *Tel.:* +1-301-594-7672; *Fax:* +1-301-435-6344; *E-mail:* wanderso@mail.nih.gov